

# HIV/AIDS

## Research Review

Making Education Easy

Issue 11 - 2009

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### Welcome to the eleventh issue of HIV/AIDS Research Review.

Two of the studies profiled in this edition discuss the proinflammatory milieu observed during treated HIV infection, resulting in an accelerated diabetogenesis and cardiac risk. Proposed strategies include therapies that reduce the inflammatory response to HIV and lowering the thresholds for treating cardiovascular risk factors in HIV-infected patients.

I hope you enjoy the latest edition and welcome your comments and feedback.

Kind regards,

Dr Tim Blackmore

[timblackmore@researchreview.co.nz](mailto:timblackmore@researchreview.co.nz)

### Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007

**Authors:** Townsend CL et al

**Summary:** Researchers from the UK and Ireland examined the outcomes of 8242 pregnancies in HIV-positive women receiving antiretroviral therapy (ART) between 1990 and 2007. The overall congenital abnormality rate was 2.8% (232/8242) and none of the abnormalities were associated with the timing of ART exposure: 2.8% (14/498) in unexposed infants, 2.7% (147/5427) following second or third trimester exposure, and 3.1% (53/1708) following first trimester exposure ( $p=0.690$ ). There was no difference in abnormality rates by class of ART exposure in the first trimester ( $p=0.363$ ), and no category of abnormality was significantly associated with timing of ART, although numbers in these groups were small. There was no increased risk of abnormalities in infants exposed to efavirenz ( $p=0.672$ ) or didanosine ( $p=0.816$ ) in the first trimester.

**Comment:** The increasing numbers of women being screened for HIV in pregnancy around the country makes the timing of this report particularly opportune. Of course the greatest number of people living with HIV/AIDS are MSM, but there are increasing numbers of women who wish to become pregnant and need antiretroviral therapy. It seems remarkable that ART seems to be so safe in pregnancy for both mother and child when one considers how the medications work. This report provides a relatively accessible source of reassurance for counselling women, particularly if they fall pregnant unexpectedly when taking ART. This is also reassuring regarding efavirenz; nevirapine is associated with liver toxicity when started in people with higher CD4 counts but has a good track record for preventing mother-to-child transmission. There were less data describing the use of efavirenz in pregnancy, and to some extent this report provides reassurance regarding its use in early pregnancy.

**Reference:** *AIDS*. 2009;23(4):519-24.

<http://www.aidsonline.com/pt/re/aids/abstract.00002030-200902200-00011.htm>

## COMING SOON to South Africa

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This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.

## Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

**Authors:** Granich RM et al

**Summary:** Universal voluntary HIV testing and immediate antiretroviral therapy (ART) for everyone diagnosed with HIV in a country with very high HIV prevalence could reduce incidence and mortality to less than one case per 1000 people per year by 2016, or within 10 years of full implementation of the strategy, and reduce the prevalence of HIV to less than 1% within 50 years, according to findings from a mathematical modelling exercise carried out by the WHO. By 2032, the estimated yearly cost of the present strategy (starting treatment at a CD4 count <350 cells/mm<sup>3</sup>) and the theoretical strategy would both be US\$1.7 billion; however, after this time, the cost of the present strategy would continue to increase whereas that of the theoretical strategy would decrease.

**Comment:** I always find mathematical modelling papers interesting; more for the assumptions than the results. This is no exception, and in many ways the conclusions must only be valid on a theoretical planet! As the authors state, they did not model the programmatic parts of the theoretical interventions. Nonetheless, I recommend this paper as a chance to think about the epidemiological aspects of HIV infection: when are people infected with HIV most likely to transmit the infection? Is treatment truly a way of reducing transmission? The idea of starting treatment at the time of diagnosis with early screening is very challenging. It brings back the debate around “hit hard and hit early” presumably mainly for the benefits of society rather than the individual this time around.

**Reference:** *Lancet*. 2009;373(9657):48-57.

<http://tinyurl.com/d3zkc8>

## Oral HIV-exposure elicits mucosal HIV-neutralizing antibodies in uninfected men who have sex with men

**Authors:** Hasselrot K et al

**Summary:** Saliva samples were collected from HIV IgG seronegative men (n=25) whose male partners were HIV infected and from low-risk healthy controls (n=22) and analysed for HIV-neutralising capacity. Of 25 exposed, uninfected individuals (EUI), 21 reported receptive unprotected oral intercourse, whereas three of the 25 reported unprotected anal receptive intercourse. Whole saliva from both EUI and low-risk healthy controls contained HIV-neutralising activity. However, a significant difference was seen when analysing the salivary IgA1 fraction: 13 of 25 EUI neutralised HIV, whereas none of the 22 controls had this capacity. The neutralising capacity of the EUI males persisted during 2 years of follow-up.

**Comment:** I try to include papers on lab science, although I am not sure how interesting they are to the readers of the *Research Review*. This is an example of an interesting observation, but I am not sure that we can quite conclude that oral sex is protective! It in many ways is not surprising that non-infected partners of HIV-infected men have IgA against HIV, it does however lead to the question whether there are novel ways of enhancing mucosal immunity. Unfortunately, so far it seems that the vaccination attempts have all been very disappointing, so observations such as this are unlikely to lead to therapeutic interventions any time soon.

**Reference:** *AIDS*. 2009;23(3):329-33.

<http://www.aidsonline.com/pt/re/aids/abstract.00002030-200901280-00006.htm>



**Independent  
commentary by  
Dr Tim Blackmore**

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## A double-blinded, randomized controlled trial of zoledronate therapy for HIV-associated osteopenia and osteoporosis

**Authors:** Huang J et al

**Summary:** To evaluate the efficacy of a single 5 mg dose of intravenous zoledronate for the treatment of HIV-associated osteopenia and osteoporosis, 30 HIV-infected men and women were assigned to zoledronate or placebo infusions and followed for 12 months on daily calcium and vitamin D supplements. At baseline, study participants had median T-scores of -1.7 for the lumbar spine and -1.4 for the hip, a median CD4 cell count of 461 cells/ $\mu$ L, 93% had HIV-RNA viral loads >400 copies/mL, and 97% were taking antiretroviral medications. Over the 12-month follow-up, absolute bone density and sex-adjusted T-scores were significantly improved from baseline in zoledronate recipients, whereas only minimal changes were observed in placebo recipients. Levels of bone resorption markers were significantly decreased over the study period in the zoledronate group compared with the placebo group.

**Comment:** This paper made me think, because I have not been particularly diligent with monitoring bone metabolism and osteoporosis in HIV-infected patients. However, as numbers increase of older people with HIV surviving malignancies such as carcinoma of the prostate, it is useful to be reminded. I will have to discuss with colleagues the pluses and minuses of intravenous versus oral bisphosphonate therapy in this situation. This is another reminder to take seriously the non-infective issues around aging and HIV. Yet again, the smoking message comes through: smoking is not good for your bones, and as people live longer they really should look after themselves with such lifestyle choices as diet, exercise and smoking. If HIV is no longer the imminent killer it used to be, the corollary is that once ART is available the lobbyists should move onto healthy lifestyles (yeah right).

**Reference:** *AIDS*. 2009;23(1):51-7.

<http://tinyurl.com/cbobgw>

## Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women

**Authors:** Hessel NA et al

**Summary:** This multisite cohort study assessed the prevalence and risk factors for anal intraepithelial neoplasia (AIN) in 470 HIV-infected women and in 185 women at risk for HIV infection. Low-grade AIN was present in 12% of HIV-infected and 5% of HIV-uninfected women, and high-grade AIN in 9% of HIV-infected and 1% of HIV-uninfected women. In adjusted analyses among HIV-infected women, the risk factors for low-grade AIN were younger age (OR, 0.59), history of receptive anal intercourse (OR, 3.2), anal human papillomavirus (HPV; oncogenic types only OR, 11; oncogenic and nononcogenic types OR, 11), and cervical HPV (oncogenic and nononcogenic types OR, 3.5). In multivariable analyses among HIV-infected women, the only significant risk factor for high-grade AIN was anal HPV infection (oncogenic and nononcogenic types OR, 7.6).

**Comment:** The whole area of AIN remains highly contentious. There are clear epidemiological links between anal HPV and high-grade AIN in men, and this is the first paper that I have seen that examined the situation in women. It is hard to determine at this stage where to go from here: in my opinion it is not possible to recommend routine screening because although there are methods described for screening the anus for AIN there are no clear treatment recommendations. The lack of data will undoubtedly change but at this stage is timely to remember that sexual health histories should always be taken, and that cervical atypia is a risk for anal atypia. Writing this review made me look further at the literature, and there are more reports of anal malignancy occurring in non-HIV-infected men and women. This area will continue to develop, but as always the issue will be of access to care. There are large numbers of women who do not access cervical screening, a primary reason for introducing the HPV vaccine. If cervical screening is hard, anal screening in a systematic way is nigh on impossible.

**Reference:** *AIDS*. 2009;23(1):59-70.

<http://tinyurl.com/cw7x8>

## Changes in cancer mortality among HIV-infected patients: the Mortalité 2005 survey

**Authors:** Bonnet F et al

**Summary:** The multinational Mortalité survey investigated the distribution of causes of death among HIV-infected patients in France in 2005 and its changes compared with a similar survey conducted in 2000. Overall, 1042 deaths were notified in 2005 (vs 964 in 2000). The most frequent underlying causes of death were an AIDS-defining illness (36% in 2005 vs 47% in 2000), cancer not related to AIDS or hepatitis (17% vs 11%), liver-related disease (15% vs 13%: hepatitis C, 11%, and hepatitis B, 2%), cardiovascular disease (8% vs 7%), suicide (5% vs 4%), and other infections (4% vs 7%). Among cases involving AIDS, the proportion of non-Hodgkin lymphoma-associated deaths did not change statistically significantly between 2000 and 2005 (11% and 10% of deaths, respectively). Cancers not related to AIDS or hepatitis were most frequently localised in the lung (31%) and digestive tract (14%). Among the liver-related deaths, 24% were due to hepatocarcinoma.

**Comment:** Malignancy represented a third of all deaths in this French cohort, with AIDS-related cancer remaining stable. In other words this is yet more evidence of normal mortality catching up with those infected with HIV: smoking, viral hepatitis and alcohol-related malignancies are all on the increase. As the management of HIV improves, the pressure shifts onto other health issues. It is no longer the case of "eat, drink and be merry (gay?) for tomorrow we die!"

**Reference:** *Clin Infect Dis*. 2009;48(5):633-9.

<http://www.journals.uchicago.edu/doi/abs/10.1086/596766>

## Motivations for the recreational use of erectile enhancing medications in urban gay and bisexual men

**Authors:** Pantalone DW et al

**Summary:** These researchers sought to characterise the associations between recent recreational erectile enhancing medication (EEM) use and illegal drug use, incident sexually transmitted infections (STIs) and unprotected sex, and report on motivations for EEM use. Data were analysed from 912 gay/bisexual men surveyed at two large lesbian, gay and bisexual community events in New York City in 2006. Lifetime EEM use was reported by 28.0% of the men; 17.4% used EEM in the past 3 months. EEM users were more likely to be white and HIV-positive. EEM users were more likely to engage in unprotected anal insertive sex with seroconcordant and serodiscordant partners. EEM users who were HIV-negative were more likely to report using alcohol and other drugs before and during sex, especially crystal methamphetamine as well as to endorse incident STIs. The most frequent responses for EEM use were to "add to the fun", "maintain an erection while using a condom" and "to have sex for hours". Men with HIV were 2.93 times more likely to endorse using EEMs to bareback.

**Comment:** I am not sure what my conclusions should be from this article. In some ways it states what seems obvious. The group surveyed clearly was not a full cross-section of the gay and bisexual community, but the results do suggest that we should have plenty of safer sex messages for those being prescribed EEM. I am still despondent that any lifestyle or behavioural message really makes much difference. I guess we have to live in the hope that some take on the message, but so far one might conclude that EEM, cigarettes, and sex without a condom should be banned!

**Reference:** *Sex Transm Infect*. 2008;84(6):458-62.

<http://sti.bmj.com/cgi/content/abstract/84/6/458>



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## Inflammatory and coagulation biomarkers and mortality in patients with HIV infection

**Authors:** Kuller LH et al

**Summary:** Stored tissue samples from participants in the Strategies for Management of Anti-Retroviral Therapy (SMART) trial were analysed for levels of six biomarkers: high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), amyloid A, amyloid P, D-dimer, and prothrombin fragment 1+2. The researchers conducted two studies: (1) a nested case-control study for studying biomarker associations with mortality, and (2) a study to compare biomarker changes between participants randomised to intermittent, CD4-guided antiretroviral therapy (ART) (drug conservation [DC]) and those on continuous ART (viral suppression [VS]). For (1), markers were determined at study entry and before death (latest level) for 85 deaths and for two controls (n=170) matched on country, age, sex, and date of randomisation. For (2), the biomarkers were assessed for 249 DC and 250 VS participants at study entry and 1 month later. Higher levels of hsCRP, IL-6, and D-dimer at study entry were significantly associated with an increased risk of all-cause mortality. Adjusted associations were significant when the DC and VS groups were analysed separately, and when latest levels were assessed. IL-6 and D-dimer levels increased at 1 month by 30% and 16% in the DC group and by 0% and 5% in the VS group ( $p < 0.0001$  for treatment difference for both biomarkers); increases in the DC group were related to HIV-RNA levels at 1 month ( $p < 0.0001$ ). In an expanded case-control analysis (four controls per case), the OR (DC/VS) for mortality was reduced from 1.8 ( $p = 0.02$ ) to 1.5 and 1.4 after adjustment for latest levels of IL-6 and D-dimer, respectively.

**Comment:** This study has been talked about at meetings and it is nice to have it in print. It shows that HIV itself induces an inflammatory state, which in turn is well described as being associated with adverse cardiac outcomes. The cardiovascular outcome data from the SMART study are robust, and this fills in some gaps, but is not surprising, given the results of SMART. The next steps of trying to reduce inflammation in my opinion are a long way off. Anti-inflammatory treatments of infection and sepsis have been disappointing in the extreme, because the inflammatory response is at least in part controlling the infection itself. Statins reduce CRP levels and other markers of inflammation and of course reduce cardiovascular mortality in those at risk of myocardial infarction. Perhaps the safest conclusion at this stage is to have a lower threshold of using them in those not taking ART and with other cardiovascular risk factors.

**Reference:** *PLoS Medicine*. 2009;5(10):e203

<http://tinyurl.com/5mucbd>

## Proinflammatory markers, insulin sensitivity, and cardiometabolic risk factors in treated HIV infection

**Authors:** Samaras K et al

**Summary:** This study compared circulating inflammatory molecules in 20 treated HIV-infected men (with and without subcutaneous lipoatrophy) in relation to insulin sensitivity, lipids total body, and intramyocellular fat, with those measured in 26 insulin-resistant obese men. C-reactive protein (CRP) levels in treated HIV were similar to those in insulin-resistant obesity, despite lower total body fat and greater insulin sensitivity in treated HIV. In HIV-lipoatrophy, CRP was higher than that found in insulin-resistant obesity. Adiponectin was similar between treated HIV and insulin-resistant obesity, but significantly lower in those with HIV-lipoatrophy. In treated HIV, subjects with higher CRP had significantly higher levels of total cholesterol, visceral adipose tissue (VAT), and intramyocellular lipids (IMCL). In treated HIV, lower adiponectin was associated with significantly lower HDL and higher levels of triglycerides, glucose, VAT, and IMCL.

**Comment:** This adds to the previous article, but adds some alarming data showing that even treated men with HIV have proinflammatory markers which correlate with cardiovascular risk. Again, I am lead to believe that the thresholds for treating cardiovascular risk factors such as cholesterol and hypertension should be lower for HIV-infected men. (This article does not provide data for women.) The presence of lipoatrophy clearly adds to the risk, so hopefully the greater use of abacavir and tenofovir, as opposed to stavudine and didanosine, will hopefully help.

**Reference:** *Obesity (Silver Spring)*. 2009;17(1):53-9.

<http://www.nature.com/oby/journal/v17/n1/abs/oby2008500a.html>

## Preclinical development of the green tea catechin, epigallocatechin gallate, as an HIV-1 therapy

**Authors:** Nance CL et al

**Summary:** This *in vitro* study investigated the inhibition of HIV-1 infectivity by the green tea catechin, epigallocatechin gallate (EGCG) in PBMCs, CD4+ T cells, and macrophages isolated from blood of HIV-1-uninfected donors. EGCG induced inhibition of HIV-1 infectivity on human CD4+ T cells and macrophages in a dose-dependent manner. At a physiological concentration of 6  $\mu\text{mol/L}$ , EGCG significantly inhibited HIV-1 p24 antigen production across a broad spectrum of both HIV-1 clinical isolates and laboratory-adapted subtypes (B [ $p < 0.001$ ], C, D, and G [ $p < 0.01$ ]). The specificity of the EGCG-induced inhibition was substantiated by the failure of EGCG derivatives lacking galloyl and/or pyrogallol side groups to alter HIV-1 p24 levels. EGCG-induced inhibition of HIV-1 infectivity was not a result of cytotoxicity, cell growth inhibition, or apoptosis.

**Comment:** I am often asked about alternative and complementary medicine approaches. Perhaps green tea should be included in "green prescriptions".

**Reference:** *J Allergy Clin Immunol*. 2009;123(2):459-65.

[http://www.jacionline.org/article/S0091-6749\(08\)02440-8/abstract](http://www.jacionline.org/article/S0091-6749(08)02440-8/abstract)

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